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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

5/16/05 DA

Office Action Summary	Application No.	Applicant(s)	
	10/615,615	KOCKEN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *11-26 and 31-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

VM

DETAILED ACTION

Acknowledgment is made of an amendment/response, filed 03/14/2005, amending claims 1-3, 5-10 and 27-30. Claims 1-44 are currently pending of which claims 11-26 and 31-44 are withdrawn from consideration as being drawn to nonelected subject matter. Claims 1-10 and 27-30 are under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn. A response to Applicant's arguments will be set forth immediately following the body of the rejections herein.

It is noted that in the previous Action, the rejection under 35 U.S.C. § 102 was inadvertently set forth under § 102 (a), instead of the correct section - § 102(b). The prior art reference (infra, Kocken et al.) has a publication date of January 1, 1999, while the earliest claim to priority in the instant application is to a foreign document (EPO 00204697.7) filed 12/22/2000, but with effective domestic priority based on a PCT filing (PCT/NL01/00934) filed 12/21/2001. It follows that the reference is published more than one year before the earliest applicable effective filing date to which priority is claimed. As such the rejection is set forth herein under 35 U.S.C. 102(b). As new grounds of rejection are set forth, this action is nonfinal.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 1-10 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

1. **Claims 1-10 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection was made previously and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More specifically the claims are directed to a genus of nucleic acid molecules that encode an AMA-1 ectodomain or a part, derivative or analogue thereof, with a single disclosed functionality – the requirement that each molecule encodes an antigen that will produce protective immunity. (e.g. Specification, p. 5, ¶ 1; p. 12, ¶ 2; p. 14, ¶ 2; p. 15, ¶ 2; p. 16, ¶ 1). In other words, the invention is directed to a genus in terms of any nucleic acid molecule encoding any portion of any Plasmodium AMA-1 ectodomain having protective immunogenic functionality.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification does not contain a sufficient number of examples of particular embodiments for such nucleic acid molecules. The instant specification provides limited guidance for one of skill to envisage the vast number of embodiments claimed.

For example, five different structures (i.e. amino acid residues 25-442, 303-442, 303-544, 419-544 and 97-545 of the sequence provided in Fig. 1) from a single species of Plasmodium (*falciparum*) are show to react with a monoclonal antibody. (Spec. pp. 24-26). Of the five only three are show to reactive with the parasite-inhibitory antibody. (e.g. p. 24, bottom ¶).

There is no further information provided to clarify the different regions or sequences (i.e. fragments, analogues or derivatives) that actually inhere the immunogenic functionality. Of course, even if such clarification were provided, it would be limited to a single species of Plasmodium, if not a single strain. (See infra, Fandeur et al. Am. J. Trop. Med. 1998; 58(2):225-31). Moreover, significance of any further clarification could be host-specific. (Id.). The disclosure provides and additional two fragments (i.e. amino acid residues 97-442 and 97-318), which are shown to have some *in vitro* inhibitory activity (i.e. antibodies to said fragments result in 50-60% inhibition of invasion).

However, even a single amino acid change in any of the disclosed structures could result in a distinct functionality in regard to the antigen eliciting protective immunity *in vivo*, notwithstanding *in vitro* results disclosed. In sum, the disclosure is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all Plasmodium AMA-1 ectodomains, functional fragments, derivatives or analogues thereof, based on the teachings in the specification.

One of skill in the art would appreciate the fact that particular Plasmodium AMA-1 ectodomains, fragments, derivatives or analogues, are not necessarily interchangeable, because there can be Plasmodium variant-, strain-specific or even host specific immunity. (e.g. Fandeur et al. Am. J. Trop. Med. 1998; 58(2):225-31; e.g. Abstract; indicating Variant- and Strain-

specific immunity in a simian species infected with *Plasmodium Falciparum*). Therefore, it logically follows, as amongst the broad number of embodiments of Plasmodium AMA-1 ectodomains claimed, there would not necessarily be any functional interchangeability.

Given the enormous breadth of the nucleic acid structures encompassed by the rejected claims, and given the limited description from the instant specification of such structures, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of nucleic acid molecules encoding a Plasmodium AMA-1 ectodomain, functional fragment, derivative or analogue. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicants arguments are summarized as follows: (1) Applicants assert that "functional part" means at least 30 base pairs, more preferably at least 200 base pairs, comprising at least one expression characteristic (Remarks, p. 15, first full paragraph; citing the Specification, p. 10, ll. 25-30); and (2) since several examples are disclosed of the genus of nucleic acids encoding a "functional" part, derivative or analogue of *any* *Plasmodium* apical membrane antigen-1 ectodomain (AMA-1), then Applicants are in possession of the claimed genus of nucleic acids in a method of producing mRNA encoding said functional equivalents to AMA-1. (Remarks, p. 15, second full paragraph).

The embodiments directed to various "functional" regions of AMA-1 encompass a genus of molecules that are not necessarily interchangeable. The claims are directed to expression of a genus of mRNA encoding AMA-1 or a "functional part", "functional derivative" or "functional analogue" of AMA-1 (i.e., collectively hereinafter as "Variants").

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966. Furthermore, the Guidelines for Written Description state:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

The essential or critical feature of the claimed process is production of particular antigens having the prescribed function of conferring protective immunity or having diagnostic value, as is further discussed herein.

The specification teaches that in *Plasmodium falciparum* the AMA-1 spans amino acid residues 25 to 545 (e.g., p. 4, last ¶). However, the claims are directed to nucleic acids encoding any portion of any AMA-1 from any *Plasmodium* species. Furthermore, even if the claims were limited to nucleic acid molecules encoding AMA-1 protein from *P. falciparum*, whereby the AMA-1 spans amino acid residues 25 to 545, the claims still encompass thousands of possible Variants within said 25 to 545 amino acid region that must correlate to a specific and eminent functionality, exclusive of mere expression of said Variants in a yeast cell.

The only disclosed functionality for said Variants is the context of providing a good target for eliciting a protective immune response or to provide a target for diagnostic purposes (e.g., Specification, p. 1, last ¶; p. 2, ll. 8-11; p. 3, l. 19; p. 4, ll. 11-12, 17-18; p. 5, ll. 8-15; p. 7, ll. 20-24). Diagnostic purposes are not particularly defined, but generally the term "diagnostic" is interpreted to mean diagnosis of disease (e.g., antibodies detect AMA-1 in an ELISA assay indicating presence of a particular parasite). In sum the expressed Variants benefit the public with the utility of providing vaccination or providing a means of disease diagnostics. In other words, the claims are not merely directed to a process of expressing various regions of the AMA-1 in a yeast cell merely for the sake of expression without more.

Furthermore, the limitation "functional part" is not substantially limited by the definition provided in the specification – at least 30 or 200 base pairs long. In other words, setting a minimum threshold does not significantly minimize the number of embodiments that comprise the genus of antigen structures. As to "functional derivatives" the encoded portion of AMA-1 is defined to mean that at least one immunogenic property of said molecule is essentially the same in kind. (e.g., p. 5, ll. 15-18).

In addition, a "functional analogue" reads on a subgenus of unrelated peptides, such as those selected through a screen of a peptide library and where said peptide comprises at least one immunogenic property of AMA-1. (e.g., p. 5, ll. 23-30). Therefore, the genus of Variants literally reads on even a single codon encoded by nucleic acids encoding the amino acid residues of *any Plasmodium* AMA-1. In other words, the Variants encompass thousands of possible structures, whereby each structure must correlate to the aforementioned immunogenic properties. Therefore, the issue is whether Applicants have disclosed or clarified a sufficient number Variants with the prescribed functionality, from any species of *Plasmodium*.

By Applicants own assertion, a mere five examples (i.e., functional parts) have been provided, which are limited to *P. falciparum*. (Specification, p. 10, ll. 16-25). Such a limited disclosure cannot be deemed sufficient to possess the genus of thousands of Variants derived from not just *P. falciparum*, but from any AMA-1 from any species of *Plasmodium*. As stated in the rejection above, protective immunity can be variant-, strain- or even host-specific. (Supra, Fandeur et al. 1998). Furthermore, even amongst the five "functional parts" provided, only three react with the antibody mAB 4G2, which binds the parasite *P. falciparum*. Therefore, depending on the antibody used in a particular ELISA and a Variant may not have any diagnostic value.

Based on the description provided and the knowledge in the art, one of skill is unable to envisage a representative number of Variants that are produced by the claimed process and that correlate to the disclosed utility of conferring protective immunity or providing disease diagnostics.

In view of the foregoing, there is insufficient justification to permit an applicant to engross a broad field where neither the disclosure or the art identify a representative number of products produced by the claimed process that have the prescribed utility. Therefore, this rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 1-3, 5-6, 9-10 and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Kocken et al. (Infect. Immun. 1999 Janurary; 67(1):43-49; see whole document).**

This rejection was made previously under 35 U.S.C. 102(a) and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The claims are directed to expression of any Plasmodium apical membrane antigen 1 (AMA-1) in yeast, such as *Pichia pastoris*. More particular claims are directed the nucleic acid encoding said ectodomain to have at least one site removed where the site could otherwise be glycosylated. The limitation, "modification" is interpreted as broadly as reasonable to read on any change/alteration of the site (e.g. enzymatic or structural).

In addition, that the AMA-1 protein expressed is approximately 83 kDa in size is interpreted, as broadly as reasonable, thus any AMA-1 protein would read on this limitation.

Kocken et al. teach expression of *P. vivax* AMA-1 in *P. pastoris* to elicit protective immunity in *Macaca mulatta* monkeys. (e.g. Abstract). More particularly, particular sites that are normally glycosylated are mutagenized so as to preclude subsequent glycosylation. (e.g. p. 44, col. 1, ¶ 3). In addition, the proteins expressed are purified through such steps as dialysis, precipitation or ion exchange chromatography. (e.g. p. 44, last ¶, bridging to col. 2). In sum, Kocken et al. anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicants assert that Kocken et al. do not disclose modification of the nucleic acid sequence such that it is optimized to match the specific frequency of codon usage of an organism of choice. Furthermore, Applicants asserts in essence that one of skill in the art would understand that codon usage *is* codon optimization, such as through use of a computer program to allow design of sequences with optimized for use in a host organism. (Remarks, p. 16).

The limitation of claims 1 and 27 recites in salient part, "[S]aid nucleic acid being *modified* to utilize said yeast cell's codon usage." (emphasis added). If one of skill were to read the relevant corresponding passages in the specification, a reasonable interpretation is that *modification* is removal of at least one glycosylation site so as to enhance expression in a particular host cell, such as yeast. Notably, the specification teaches that the nucleic acids encoding AMA-1 is modified so as to utilize a yeast's codon usage. (e.g., p. 10, ll. 11-12). Most notably, the specification teaches that said modification includes removal of at least one site that is generally glycosylated by a eukaryotic expression system. (e.g., p. 9, ll. 21-30; p. 3, ll. 1-11).

With respect to "codon optimization" utilizing a computer software program such as CODOP, the claims are not exclusively limited to such an embodiment. Indeed, as stated in the foregoing, the specification teaches modification in the context of "codon usage" to mean removal of a glycosylation site. The limitation "codon usage" is interpreted as broadly as reasonable in light of the instant disclosure's teachings to mean modification of a nucleic acid to utilize a yeast cell's codon usage to enhance expression. Therefore, as stated above, Kocken et al. teaches a nucleic acid that is modified to utilize the *P. pastoris* codon usage. (e.g., p. 44, col. 1, ¶ 3). In sum, there is a discord between the totality of the instant disclosure and Applicant's suggestion that "codon usage" is limited to nonrandom utilization of synonymous codons for enhanced expression. It follows, that the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. **Claims 1-10 and 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kocken et al., and further in view of Withers-Martinez et al. (Protein Engineering. 1999; 12(12): 1113-1120; see entire document).**

This is a new ground of rejection. The claims are interpreted consonant with what is stated above. Furthermore, the teachings of Kocken et al. are interpreted and applied consonant with what is stated above. The claims are directed to a process for expression of AMA-1 or Variants thereof, from any *Plasmodium*, wherein the nucleic acid encoding said AMA-1 are modified to utilize a yeast cell's codon usage. As stated above the teachings of Kocken et al. meet all the claimed limitation.

However, insofar as codon usage can be read to also encompass synonym codon optimization for expression of heterologous proteins in a host cell (e.g., host cell codon bias), Kocken et al. does not explicitly teach expression of AMA-1 proteins where nucleic acids encoding codons are substituted for favorable synonymous codons based on the codon bias of a host cell.

Withers-Martinez et al. teach that genes from the A+T-rich genome of *P. falciparum* encodes genes of biological importance that cannot be expressed efficiently in heterologous eukaryotic systems such as *Pichia pastoris*. (e.g., Abstract; p. 1113, Introduction). The reference teaches that by designing *P. falciparum* genes (e.g., *pfsub-1*) with codon optimization in favor of the codon bias of the yeast cells, expression of can be enhanced. (e.g., p. 1113, col. 2, bottom half).

Furthermore, the reference teaches that computer programs such as CODOP are available to *inter alia* provide functions for codon optimization of a gene based on host organism preference. (e.g., p. 1114, col. 1, bottom half, bridging to col. 2, ¶ 1; p. 1115, Table I). Notably, the gene encoding *P. falciparum* AMA-1 is also A+T-rich and difficult to express in heterologous eukaryotic systems and is biologically important as is taught by Kocken et al.

Therefore, it would have been *prima facie* obvious to modify the gene encoding *P. falciparum* as taught by Kocken et al. with the codon optimization method as taught by Withers-Martinez et al. One of skill in the art in studying the two references would have been motivated optimize the gene encoding AMA-1 to obtain enhanced expression in *P. pastoris* – the expression system used in both reference and in the instant application. Given the level of skill in the art, there would have been a reasonable expectation of success to make such a modification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday, from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center at 866-217-9197 (toll-free).

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER